

What is Claimed Is:

1. A method for producing an oligonucleotide-protein conjugate, wherein said method comprises the steps:

- (A) contacting an oligonucleotide having an amino group with a heterofunctional linker, wherein said linker has a first group reactive with said amino group and a second group reactive with a thiol group, said contacting being under conditions sufficient to permit said first group of said heterofunctional linker to become bonded to said amino group of said oligonucleotide, thereby forming an oligonucleotide-heterofunctional linker conjugate; and
- (B) contacting said oligonucleotide-heterofunctional linker conjugate (A) with a protein having a thiol group reactive with said second group of said heterofunctional linker; said contacting being under conditions sufficient to permit said thiol group of said protein to become bonded to said second group of said heterofunctional linker of said oligonucleotide-heterofunctional linker conjugate, to thereby form said oligonucleotide-protein conjugate.

2. The method of claim 1, wherein said amino group is at the 3' end of said oligonucleotide.
3. The method of claim 1, wherein step (A) additionally comprises forming said oligonucleotide having said 3' amino group.
4. The method of claim 2, wherein said oligonucleotide having said 3' amino group is formed by synthesizing said oligonucleotide on a 3'-amino CPG solid support.
5. The method of claim 1, wherein said amino group is at the 5' end of said oligonucleotide.

6. The method of claim 1, wherein step (A) additionally comprises forming said oligonucleotide having said 5' amino group.
7. The method of claim 1, wherein said amino group is at an internal site of said oligonucleotide.
- 5 8. The method of claim 7, wherein step (A) additionally comprises forming said oligonucleotide having said internal amino group.
9. The method of claim 1, wherein said modified amino group is C7 CPG.
- 10 10. The method of claim 1, wherein said first group of said heterofunctional linker is an NHS group.
11. The method of claim 1, wherein said second group of said heterofunctional linker is a maleimide group.
- 15 12. The method of claim 1, wherein said heterofunctional linker is selected from the group consisting of Sulfo-SMCC; Sulfo-EMCS; Sulfo-GMBS; Sulfo-KMUS; Sulfo-MBS; Sulfo-SIAB; Sulfo-SMPB; Sulfo-LC-SMPT; SVSB; SIACX; SIA, SIAXX; and NPJA.
13. The method of claim 12, wherein said heterofunctional linker is sulfo-SMCC.
- 20 14. The method of claim 1, wherein said thiol group of said protein is derived from an iminothiolane moiety.
15. The method of claim 1, wherein step (B) additionally comprises forming said protein having said thiol group.
16. The method of claim 15, wherein said protein is formed by reacting the amino group of a protein with iminothiolane.

17. The method of claim 1, wherein said protein is an enzyme, hapten, immunoglobulin, streptavidin, avidin, or a phycobillin protein.
18. The method of claim 17, wherein said protein is an enzyme.
19. The method of claim 18, wherein said enzyme is selected from the group consisting of alkaline phosphatase, β -galactosidase, horse radish peroxidase, and urease.
20. The method of claim 17, wherein said protein is a hapten.
21. The method of claim 17, wherein said protein is an immunoglobulin.
22. The method of claim 21, wherein said immunoglobulin is an immunoglobulin that is able to bind to a drug, a receptor, a receptor ligand, or a tumor antigen.
23. The method of claim 21, wherein said immunoglobulin is able to bind an antigen that is characteristic of a pathogen.
24. The method of claim 23, wherein said pathogen is a virus.
25. The method of claim 24, wherein said pathogen is a bacteria or fungus.
26. The method of claim 17, wherein said protein is a streptavidin protein.
27. The method of claim 17, wherein said protein is an avidin protein.
28. The method of claim 17, wherein said protein is a phycobillin protein.
29. An oligonucleotide-protein conjugate produced through the process comprising:
- (A) contacting an oligonucleotide having an amino group with a heterofunctional linker, wherein said linker has a first group

reactive with said amino group and a second group reactive with a thiol group, said contacting being under conditions sufficient to permit said first group of said heterofunctional linker to become bonded to said amino group of said oligonucleotide, thereby forming an oligonucleotide-heterofunctional linker conjugate; and

(B) contacting said oligonucleotide-heterofunctional linker conjugate (A) with a protein having a thiol group reactive with said second group of said heterofunctional linker; said contacting being under conditions sufficient to permit said thiol group of said protein to become bonded to said second group of said heterofunctional linker of said oligonucleotide-heterofunctional linker conjugate, to thereby form said oligonucleotide-protein conjugate.

30. The oligonucleotide-protein conjugate of claim 29, wherein said amino group is at the 3' end of said oligonucleotide.
31. The oligonucleotide-protein conjugate of claim 29, wherein said amino group is at the 5' end of said oligonucleotide.
32. The oligonucleotide-protein conjugate of claim 29, wherein said amino group is at an internal site of said oligonucleotide.
33. The oligonucleotide-protein conjugate of claim 29, wherein said protein is an enzyme, hapten, immunoglobulin, streptavidin, avidin, or a phycobillin protein.
34. The oligonucleotide-protein conjugate of claim 33, wherein said protein is an enzyme.
35. The oligonucleotide-protein conjugate of claim 34, wherein said enzyme is selected from the group consisting of alkaline phosphatase, β -galactosidase, horse radish peroxidase, and urease.

- 36 The oligonucleotide-protein conjugate of claim 33, wherein said protein is a hapten.
37. The oligonucleotide-protein conjugate of claim 33, wherein said protein is an immunoglobulin.
- 5 38. The oligonucleotide-protein conjugate of claim 37, wherein said immunoglobulin is an immunoglobulin that is able to bind to a drug, a receptor, a receptor ligand, or a tumor antigen.
- 10 39. The oligonucleotide-protein conjugate of claim 37, wherein said immunoglobulin is able to bind an antigen that is characteristic of a pathogen.
40. The oligonucleotide-protein conjugate of claim 39, wherein said pathogen is a virus.
41. The oligonucleotide-protein conjugate of claim 39, wherein said pathogen is a bacteria or fungus.
- 15 42. The oligonucleotide-protein conjugate of claim 33, wherein said protein is a streptavidin protein.
43. The oligonucleotide-protein conjugate of claim 33, wherein said protein is an avidin protein.
- 20 44. The oligonucleotide-protein conjugate of claim 33, wherein said protein is a phycobillin protein.
45. A method for determining the presence or concentration of a target nucleic acid molecule in a sample which comprises:
- 25 (I) contacting said sample with an oligonucleotide-protein conjugate, wherein a sequence of an oligonucleotide portion of said conjugate is selected to be able to hybridize with said target nucleic acid molecule, wherein said oligonucleotide-protein conjugate is produced through the process comprising:

- (A) contacting an oligonucleotide having an amino group with a heterofunctional linker, wherein said linker has a first group reactive with said amino group and a second group reactive with a thiol group, said contacting being under conditions sufficient to permit said first group of said heterofunctional linker to become bonded to said amino group of said oligonucleotide, thereby forming an oligonucleotide-heterofunctional linker conjugate; and
- (B) contacting said oligonucleotide-heterofunctional linker conjugate (A) with a protein having a thiol group reactive with said second group of said heterofunctional linker; said contacting being under conditions sufficient to permit said thiol group of said protein to become bonded to said second group of said heterofunctional linker of said oligonucleotide-heterofunctional linker conjugate, to thereby form said oligonucleotide-protein conjugate;
- (II) detecting a protein portion of any of said oligonucleotide-protein conjugate having an oligonucleotide portion hybridized to said target nucleic acid molecule; wherein said detection determines the presence or concentration of said target nucleic acid molecule in said sample.

46. The method of claim 45, wherein said amino group is at the 3' end of said oligonucleotide.
47. The method of claim 45, wherein said amino group is at the 5' end of said oligonucleotide.
48. The method of claim 45, wherein said amino group is at an internal site of said oligonucleotide.

49. The method of claim 45, wherein said protein of said oligonucleotide-protein is an enzyme, hapten, immunoglobulin, streptavidin, avidin, or a phycobillin protein.
50. The method of claim 49, wherein said protein is an enzyme.
- 5 51. The method of claim 50, wherein said enzyme is selected from the group consisting of alkaline phosphatase, β -galactosidase, horse radish peroxidase, and urease.
52. The method of claim 49, wherein said protein is a hapten.
53. The method of claim 49, wherein said protein is an immunoglobulin.
- 10 54. The method of claim 53, wherein said immunoglobulin is an immunoglobulin that is able to bind to a drug, a receptor, a receptor ligand, or a tumor antigen.
55. The method of claim 53, wherein said immunoglobulin is an immunoglobulin that is able to an antigen that is characteristic of a pathogen.
- 15 56. The method of claim 55, wherein said pathogen is a virus.
57. The method of claim 55, wherein said pathogen is a bacteria or fungus.
58. The method of claim 45, wherein said target nucleic acid molecule is a nucleic acid molecule of a pathogen.
- 20 59. The method of claim 45, wherein said target nucleic acid molecule is a nucleic acid molecule of a tumor cell.
60. The method of claim 49, wherein said protein is a streptavidin protein.
- 25 61. The method of claim 49, wherein said protein is an avidin protein.

62. The method of claim 49, wherein said protein is a phycobillin protein.

63. A method for determining the presence or concentration of a target analyte in a sample which comprises:

- 5 (I) contacting said sample with an oligonucleotide-protein conjugate, wherein a protein portion of said conjugate is selected to be able to bind to said target analyte, wherein said oligonucleotide-protein conjugate is produced through the process comprising:
- 10 (A) contacting an oligonucleotide having a 3' amino group with a heterofunctional linker, wherein said linker has a first group reactive with said 3' amino group and a second group reactive with a thiol group, said contacting being under conditions sufficient to permit said first group of said heterofunctional linker to become bonded to said 3' amino group of said oligonucleotide, thereby forming an oligonucleotide-heterofunctional linker conjugate; and
- 15 (B) contacting said oligonucleotide-heterofunctional linker conjugate (A) with a protein having a thiol group reactive with said second group of said heterofunctional linker; said contacting being under conditions sufficient to permit said thiol group of said protein to become bonded to said second group of said heterofunctional linker of said oligonucleotide-heterofunctional linker conjugate, to thereby form said oligonucleotide-protein conjugate;
- 20 (II) detecting an oligonucleotide portion of any of said oligonucleotide-protein conjugate having a protein portion bound to said target analyte; wherein said detection
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determines the presence or concentration of said target analyte
in said sample.

64. The method of claim 63, wherein said amino group is at the 3' end of
said oligonucleotide.
- 5 65. The method of claim 63, wherein said amino group is at the 5' end of
said oligonucleotide.
66. The method of claim 63, wherein said amino group is at an internal
site of said oligonucleotide.
- 10 67. The method of claim 63, wherein said protein of said oligonucleotide-
protein is an enzyme, receptor or receptor ligand.
68. The method of claim 67, wherein said protein is an enzyme.
- 69 The method of claim 67, wherein said protein is a receptor.
- 70 The method of claim 67, wherein said protein is a receptor ligand.
71. The method of claim 67, wherein said protein is a tumor antigen.
- 15 72. The method of claim 53, wherein said protein is characteristic of a
pathogen.
73. The method of claim 72, wherein said pathogen is a virus.
74. The method of claim 72, wherein said pathogen is a bacteria or
fungus.